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UNITED STATES BANKRUPTCY COURT
SOUTHERN DISTRICT OF NEW YORK

In re:	:	Chapter 11
PURDUE PHARMA L.P., *et al*.,	:	Case No. 19-23649 (RDD)
Debtors.[1]	:	(Jointly Administered)

NAS AD HOC COMMITTEE'S NOTICE OF REFILING OF CERTAIN DOCUMENTS ON THE PUBLIC DOCKET RECORDS

The NAS Children Ad Hoc Committee (the "**NAS Committee**"), by and through its undersigned counsel, Tarter Krinsky & Drogin LLP, respectfully submits this Notice of Refiling of Certain Documents on the Public Record (the "**Notice**"):

[1] The Debtors in these cases, along with the last four digits of each Debtor's registration number in the applicable jurisdiction, are as follows: Purdue Pharma L.P. (7484), Purdue Pharma Inc. (7486), Purdue Transdermal Technologies L.P. (1868), Purdue Pharma Manufacturing L.P. (3821), Purdue Pharmaceuticals L.P. (0034), Imbrium Therapeutics L.P. (8810), Adlon Therapeutics L.P. (6745), Greenfield BioVentures L.P. (6150), Seven Seas Hill Corp. (4591), Ophir Green Corp. (4594), Purdue Pharma of Puerto Rico (3925), Avrio Health L.P. (4140), Purdue Pharmaceutical Products L.P. (3902), Purdue Neuroscience Company (4712), Nayatt Cove Lifescience Inc. (7805), Button Land L.P. (7502), Rhodes Associates L.P. (N/A), Paul Land Inc. (7425), Quidnick Land L.P. (7584), Rhodes Pharmaceuticals L.P. (6166), Rhodes Technologies (7143), UDF L.P. (0495), SVC Pharma L.P. (5717) and SVC Pharma Inc. (4014). The Debtors shall include their affiliates and other entities under their control. The Debtors' corporate headquarters is located at One Stamford Forum, 201 Tresser Boulevard, Stamford, CT 06901.

Recitals

A. On December 15, 2020, the NAS Committee filed under seal its motion seeking discovery from the Debtors, pursuant to Bankruptcy Rule 2004, along with supporting exhibits and material (the "Rule 2004 Motion").[2]

B. On December 18, 2020, the Debtors filed their objection to the NAS Committee's Rule 2004 Motion. [3] The Debtors and the NAS Committee met and conferred, on December 21, 2020, and reached an agreed path forward with respect to the NAS Committee's Rule 2004 Motion, which was conveyed to this Court on December 22, 2020.[4]

C. On March 19, 2021, the NAS Committee filed under seal its reply in further support of the Rule 2004 Motion, along with supporting exhibits and material (the "Rule 2004 Reply")[5]. On April 1, 2021, the Debtors filed their statement in response to the NAS Committee's Rule 2004 Reply and the McClammy Declaration[6].

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[2] See, *The NAS Children Ad Hoc Committee's Motion Entry of Order Pursuant to 11 U.S.C. §§ 105(A) and 107(B) and Fed. R. Bankr. P. 9018 Authorizing the Filing of Certain information and Exhibits Under Seal in Connection with the NAS Children Ad Hoc Committee's Ex Parte Motion Requesting a Court Order Authorizing Examinations Pursuant to Federal Rules of Bankruptcy Procedure 2004 and 9006* (Dec. 15, 2020), Dkt. No. 2139.

[3] See, *Debtors' Objection to the NAS Children Ad Hoc Committee's Motion Entry of Order Pursuant to 11 U.S.C. §§ 105(A) and 107(B) and Fed. R. Bankr. P. 9018 Authorizing the Filing of Certain information and Exhibits Under Seal in Connection with the NAS Children Ad Hoc Committee's Ex Parte Motion Requesting a Court Order Authorizing Examinations Pursuant to Federal Rules of Bankruptcy Procedure 2004 and 9006* (Dec. 18, 2020), Dkt. No. 2155.

[4] See, *Declaration of James I. McClammy in Support of the Debtors' Statement in Response to the Reply of the NAS Children Ad Hoc and Supplemental Declaration in Further Support of its Request for Entry of a Court Order Authorizing Examinations Pursuant to Federal Rules of Bankruptcy Procedure 2004 and 9006,* Ex. 10 (Apr. 1, 2021), Dkt. No. 2585 (The **"McClammy Declaration**").

[5] See, *The NAS Children Ad Hoc Committee's Motion Entry of Order Pursuant to U.S.C. §§ 105(A) and 107(B) and Fed. R. Bankr. P. 9018 Authorizing the Filing of Certain information and Exhibits Under Seal in Connection with the Reply and Supplemental Declaration in Further Support of NAS Children Ad Hoc Committee's Ex Parte Motion Requesting a Court Order Authorizing Examinations Pursuant to Federal Rules of Bankruptcy Procedure 2004 and 9006* (Mar. 19, 2021), Dkt. No. 2538.

[6] See, *Debtors' Statement in Response to the Reply of the NAS Children Ad Hoc and Supplemental Declaration in Further Support of its Request for Entry of a Court Order Authorizing Examinations Pursuant to Federal rules of Bankruptcy Procedure 2004 and 9006* (Apr. 1, 2021), Dkt. No. 2584.

D. On June 7, 2021, in accordance with the Third Amended Protective Order, the NAS Committee sent the Debtors an email challenging the designation of certain documents, most of which the NAS Committee filed under seal in connection with its Rule 2004 Motion and Rule 2004 Reply (the "Challenge Notice")[7]. On June 11, 2021, the Debtors responded to the Challenge Notice, offering to modify the designation of certain documents and explaining the basis of the designation for the remaining documents. On June 18, 2021, the NAS Committee sent a letter to this Court challenging the designation of the documents (the "Challenge Letter"), and on June 23, 2021, the Debtors submitted their response to the Challenge Letter.

E. On June 24, 2021, the Debtors and the NAS Committee agreed to continue to meet and confer regarding the issues raised by the NAS Committee in the Challenge Letter. As a result of continued meet and confers, the Debtors and the NAS Committee had reached an agreement with respect to the unsealing of certain materials filed in connection with the NAS Committee's Rule 2004 Motion and Rule 2004 Reply that are also the subject of the Challenge Letter; the agreement was reduced to a stipulation and agreed order that had been duly presented to the Court and 'so ordered' on October 15, 2021.[8]

F. Accordingly, the NAS Ad Hoc Committee hereby refile on the public docket the following set of materials subject to the Order:

1. E513_00045970- Mundipharma Swedish SMPC- Opidol 6.17.03 Final Version.
2. E513_00046100- Mundipharma Swedish SMPC- Opidol 12-17-04.
3. PURCHI-000572404- Archival NDA 1994 Section E.3
4. PPLPRO01000394434- 2003 CCDS Revisions.
5. PPLPC028000094094- 10-2-03 Emails.
6. OAK0568468- 6/8/2000 Sackler Emails.
7. E01_00002130- Response to FDA Inquiries.
8. E513_00114030- Table for FDA Response.

[7] See, *Third Amended Protective Order*, ¶ 65 (Nov. 12, 2020), Dkt. No. 1935.
[8] See, *So Ordered Stipulation and Agreed Order Regarding Unsealing of Certain Materials Filed in Connection With The NAS Children Ad Hoc Committes' Rule 2004 Motion and Reply* (Oct. 15, 2021), Dkt. No. 3960.

Dated: November 18, 2021
New York, New York

TARTER KRINSKY & DROGIN LLP
Counsel for NAS Ad Hoc Committee

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Exhibit 1

Summary of Product Characteristics

1 NAME OF MEDICINAL PRODUCT

Opidol Uno, 12 mg, 16 mg, 24 mg and 32 mg prolonged release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 prolonged release capsule contains hydromorphone hydrochloride 12 mg, 16 mg, 24 mg and 32 mg corresponding to 10.7 mg, 14.2 mg, 21.4 mg and 28.4 mg hydromorphone, respectively.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard

Opidol Uno 12 mg capsules are rust, opaque capsules marked P-XL 12 mg.
Opidol Uno 16 mg capsules are flesh-coloured opaque capsules marked P-XL 16 mg.
Opidol Uno 24 mg capsules are powder blue, opaque capsules marked P-XL 24 mg.
Opidol Uno 32 mg capsules are white opaque capsules marked P-XL 32 mg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Long-term, severe opioid-sensitive pain, such as cancer pain.

4.2 Posology and method of administration

The capsules should be swallowed whole or the capsules may be opened and the content sprinkled on semisolid food and consumed immediately after. The content of the capsules must not be crushed, chewed or dissolved. Taking chewed, crushed or dissolved Opidol Uno capsules or its contents can lead to the rapid release and absorption of a potential fatal dose of hydromorphone.
Opioids must be dose-titrated individually because of the wide differences between different patients with regard to pharmacokinetics, intensity and genesis of pain, possible tolerance and age. The therapy is started by titration with a short-acting hydromorphone capsule to a dose of hydromorphine that gives freedom from pain.

Adults: Administered every 24 hours.The dose must be adjusted individually to the condition of the patient, taking into account any previous pain therapy.
12 mg of hydromorphone has an analgesic efficacy equivalent to 90 mg of morphine sulphate given orally.
An opioid naive patient with severe uncontrolled pain must be titrated with immediate release hydromorphone (e.g. Opidol capsules) before conversion to Opidol Uno prolonged release capsules. Increasing severity of pain will require increased dosage to achieve the desired relief.

Elderly: Dose reduction should be considered.

Children: Not recommended for children aged below 18.

Patients with impaired renal or liver function: As available data on these groups of patients are limited, treatment should begin with the lowest possible dose and the patients must be monitored regularly. Further adjustments to the dose should be made with caution.

For switching from another peroral or parenteral opioid therapy to Opidol Uno prolonged release capsules the conversion table shown below is intended for use as a guideline. The previous daily dose is multiplied by the factor for the opioid used in order to obtain the daily dose of Opidol capsules.No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses are only a starting point, and close observation and frequent titration is indicated until a satisfactory dose is obtained on the new therapy.

Opioid	*Peroral*	*Parenteral*
Morphine, acute treatment	0.13	0.8
Morphine, chronic treatment	0.13	0.4
Ketobemidone	0.13	0.4
Methadone	0.4	0.8
Pethidine	0.03	0.11
Hydromorphone	1	
Oxycodone	0.25	

4.3 Contraindications

Respiratory depression with hypoxia or elevated carbon dioxide levels in the blood, paralytic ileus, convulsions, stasis of secretion, coma, acute abdominal pain, seriously impaired liver function, hypersensitivity to hydromorphone or other ingredients in the capsules, anxiety states under the influence of alcohol or hypnotics. Concurrent administration of monoamine oxidase inhibitors or administration within 2 weeks after discontinuation of their use. Use of Opidol Uno prolonged release capsules should be avoided in patients with raised intracranial pressure or head injury.

Pre-operative administration of Opidol Uno prolonged release capsules is not recommended

4.4 Special warnings and precautions for use

The most serious risk of opioid excess is respiratory depression. Caution should be exercised in pulmonary disease, especially with airflow obstruction (see also section 4.3 "Contra-indications"). As with all narcotics, the drug should be used with caution in the elderly and infirm or patients with hypothyroidism, impaired renal or liver function or adrenocortical failure, prostate hypertrophy, Addison's disease, toxic psychosis, delirium tremens, pancreatitis, shock or reduced pulmonary capacity, reduction of the dose should be considered.

Opidol Uno prolonged release capsules are not recommended in the first 24 hours post-operatively. After this time they should be used with extreme caution, particularly following abdominal surgery. Opidol Uno prolonged release capsules should not be used if there is a risk of paralytic ileus. Should paralytic ileus be suspected or occur during use, the treatment should be discontinuedWhere patients are to undergo cordotomy or other surgical procedure for pain relief, the therapy should be discontinued 24 hours before the operation. If further treatment with Opidol Uno prolonged release capsules is indicated, the dosage should be adjusted to the new post-operative requirement. Drug tolerance may develop in long-term use. Hydromorphone has a morphine like abuse potential. The medication should be discontinued gradually after long-term use in order to avoid withdrawal symptoms

4.5 Interactions with other medicinal products and other forms of interaction

Opidol Uno prolonged release capsules should not be co-administered with monoamine oxidase inhibitors or within two weeks of discontinuation of their use (see section 4.3 "Contra-indications"). Opidol Uno prolonged release capsules potentiate the effects of tranquillisers, anaesthetics, hypnotics and sedatives. Use of any of these pharmaceuticals in combination with Opidol Uno prolonged release capsules, may cause potentiation of the effect of either drug e.g.

sedation or respiratory depression. The patient should be watched over, and a reduction of the dose may be necessary.

4.6 Pregnancy and lactation

Pregnancy: There is no experience of therapy during pregnancy. In animals, no teratogenic effects were noted in rats at doses up to 10 mg/kg, or in rabbits at doses up to 50 mg/kg. Maternal toxicity was observed in both studies. Exposures were at least 1.8 (rat) and 8 (rabbit) times the anticipated human exposure based on AUC from a 32 mg daily oral dose of hydromorphone in humans.

During pregnancy hydromorphone should be given only on strict indications and when the need of the mother has been weighed against the risks to the child. In the event of long-term therapy during pregnancy the risk of neonatal abstinence should be considered.

Analgesics of opioid type may cause neonatal respiratory depression. For 2-3 hours before expected delivery hydromorphone should be given only on strict indications and when the need of the mother has been weighed against the risks to the child.

Lactation: The passage of hydromorphone to breast milk has not been studied. Women should not breastfeed while being treated with hydromorphone.

4.7 Effects on ability to drive vehicles and use machines

Treatment with Opidol Uno prolonged release capsules may impair reactive ability. This should be borne in mind when keen attention is required, e.g. when driving.

4.8 Undesirable effects

The commonest side effects are constipation, nausea, vomiting. Constipation may be treated with appropriate laxatives. When nausea and vomiting present a problem, Opidol Uno prolonged release capsules may be combined with antiemetics.

Central Nervous system	
Very common (≥ 10%)	Asthenia, dizziness, somnolence.
Common (≥ 1%)	Confusion, physical dependence, hallucination.
Uncommon (< 1%)	Abuse, agitation, addiction, blurred vision, drowsiness, dysphoria, euphoria, headache, miosis, myoclonus, sedation, seizure.
Vascular	
Common (≥ 1%)	Hypotension.
Respiratory	
Uncommon (< 1%)	Respiratory depression.
Gastrointestinal	
Very common (≥ 10%)	Constipation, nausea, vomiting.
Common (≥ 1%)	Dry mouth.
Uncommon (< 1%)	Biliary spasm, ileus.

Dermatologic	
Very common (≥ 10%)	Pruritus
Common (≥ 1%)	Rash, sweating.
Uncommon (< 1%)	Urticaria.
Renal and urinary disorders	
Common (≥ 1%)	Urinary retention

Drowsiness usually abates after a few days' administration. Spasms in the bile duct and urinary tract may arise in predisposed individuals. The respiratory-depressive effect is dose-dependent and seldom constitutes a clinical problem.

4.9 Overdosage

Indications of overdosage are miosis, respiratory depression and low blood pressure. Circulatory disorders and coma may occur in serious cases and may be fatal. Treatment:
Primary attention should be given to the establishment of clear airways and institution of assisted or controlled ventilation.

In case of massive overdose, naloxone 0.8 mg is administered intravenously. Repeat at 2-3 minutes intervals as necessary, or by an infusion of 2 mg in 500 mg of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Opidol Uno prolonged release capsules will continue to release hydromorphone for up to 12 24 hours after administration. Treatment of the overdose should be adjusted accordingly.

For less severe overdose, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant or circulatory depression secondary to morphine overdose.

Naloxone should be administered cautiously to patients who are known, or suspected, to be physically dependent on hydromorphone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

It may be necessary to empty the stomach to remove non-absorbed drug, especially in the case of prolonged release capsules.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Narcotic analgesic, ATC-code N02AA03.

Hydromorphone is structurally related with morphine. At analgesic doses hydromorphone and morphine have comparable pharmacological profiles. The analgesic effect is due in part to a changed pain perception and in part to an elevation of the pain threshold. With oral administration the ratio of analgesic potency between hydromorphone and morphine is approximately 7.5:1.
Hydromorphone 12 mg has an analgesic effect equivalent to approx. 90 mg morphine sulphate with peroral administration.
The central nervous system effects of hydromorphone also include respiratory depression, mental symptoms, nausea and vomiting, miosis and release of antidiuretic hormone.
The respiratory-depressive effect of hydromorphone is due in part to an inhibition of the stimulating effect of carbon dioxide on the respiratory centre in the medulla oblongata. This effect may lead to respiratory insufficiency in patients with impaired ability to ventilate as a result of pulmonary disease or the effect of other drugs.

Intoxication with hydromorphone requires respiratory-support therapy and the administration of antidote.
Mental symptoms include euphoria, but also depression, sleeplessness, and disturbances of concentration and memory.

Stimulation of dopamine receptors in the "trigger zone" in the medulla oblongata may give rise to nausea and vomiting. The increased release of anti-diuretic hormone contributes to a reduction in urine volumes during hydromorphone therapy. Hydromorphone increases tone in the smooth muscles of the gastrointestinal canal. This leads to constipation as a result of slower passage of food through the gastrointestinal canal. Pressure in the biliary and urinary ducts also rises, making hydromorphone less appropriate in cases of biliary or urethral spasm.

Hydromorphone has habit-forming characteristics similar to morphine. Tolerance to the effects of hydromorphone may develop over time. However this does not usually cause any problems in the treatment of severe pain such as cancer pain.

5.2 Pharmacokinetic properties
Hydromorphone is absorbed from the gastrointestinal canal and undergoes a first-pass metabolism. Average bioavailability is 32%. Hydromorphone is metabolized and excreted in the urine mainly in conjugated form, but also to a smaller amount as unchanged hydromorphone, dihydroisomorphine and dihydromorphine. Opidol Uno Prolonged release capsules give therapeutic plasma levels at administration every 24 hours .

Studies in healthy volunteers have demonstrated that the administration of Opidol Uno prolonged release capsules result in plasma hydromorphone concentrations that attain an initial peak within 2 to 4 hours after dosing, followed by a broad secondary peak/plateau which helps to maintain relatively constant plasma concentrations for at least 24 hours after dosing. At steady state, the availability of hydromorphone from Opidol Uno prolonged release capsules was equivalent to that provided by immediate release hydromorphone over a 24-hour period, and this was accompanied by lesser fluctuation from the once-a-day preparation. Sprinkling the contents of the capsule over a soft food had no effect on the plasma profile, providing an alternative option to patients with difficulty in swallowing.

Studies involving immediate and twice-daily hydromorphone preparations have indicated that the pharmacokinetics are linear across a wide dosage range. Dose-proportionality studies involving Opidol Uno prolonged release capsules strengths from 12 mg to 32 mg have confirmed a linearity of pharmacokinetic response.

A steady state pharmacokinetic study in healthy volunteers has indicated that the once-daily administration of Opidol Uno prolonged release capsule 12 mg provided an availability of hydromorphone equivalent to that of Palladone SR (twice-daily) 6 mg. The Opidol Uno prolonged release capsule 12 mg provided peak and trough concentrations within the range defined by Palladone SR 6 mg bd.

5.3 Preclinical safety data

Hydromorphone is structurally related to morphine and is a metabolite of morphine, codeine and dihydrocodeine. The toxicology of morphine is better known than of hydromorphone. Considering the available data, it is reasonable to conclude that the "risk - benefit" ratio is the same for hydromorphone and morphine in the treatment of chronic severe pain.
Hydromorphone was non-mutagenic in Ames test and the mouse micronucleus assay.

Hydromorphone was also non-mutagenic in the mouse lymphoma assay in the absence of exogenous metabolism. A positive response was observed in the mouse lymphoma assay in the presence of exogenous metabolism (S-9) at higher concentrations (≥200 µg/mL). Studies of hydromorphone evaluating the carcinogenic potential have not been conducted.

There were no treatment-related effects on mating, fertility, or litter parameters (eg, viability, weight, and sex ratio) at doses up to 5 mg/kg/day. The fertility and reproductive no-observable-effect-level (NOEL) of hydromorphone HCl was greater than 5 mg/kg/day (the highest dose tested).

In animals, no teratogenic effects were noted in rats at doses up to 10 mg/kg, or in rabbits at doses up to 50 mg/kg. Maternal toxicity was observed in both studies. Exposures were at least 1.8 (rat) and 8 (rabbit) times the anticipated human exposure based on AUC from a 32 mg daily oral dose of hydromorphone in humans. However, teratogenic activity with hydromorphone has been reported in the literature with mouse and hamster at oral doses of 5 mg/kg (15 mg/m^2) and 19 mg/kg (118 mg/m^2), respectively, which would be approximately equivalent to 0.7 and 5.5 times a single human oral hydromorphone dose of 32 mg.

In the perinatal/postnatal study, body weight gain and absolute and relative feed consumption values were reduced in the 2 and 5 mg/kg/day of hydromorphone F_0 groups during the gestation and lactation periods. Peripartum/postpartum pup (F_1) mortality was increased at 2 and 5 mg/kg/day and body weights were reduced during the lactation period. No statistically significant or biologically important differences in fertility, mating, the values for learning, short-term retention, long-term retention, or response inhibition in the F_1 animals at doses as high as 5 mg/kg/day of hydromorphone. The developmental NOEL for the study was 0.5 mg/kg/day of hydromorphone.

6 PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Eudragit RS PO; ethylcellulose; silica, stearyl alcohol.

Capsule shell: Gelatin, sodium lauryl sulphate, colloidal anhydrous silica.
Colouring matters:
12 mg capsules: Titanium dioxide (E171), iron oxide (E172)
16 mg capsules: Titanium dioxide (E171), iron oxide (E172)
24 mg Capsules: Titanium dioxide (E171), Indigotin I (E132)
32 mg capsules: Titanium dioxide (E171)

Ink:
Shellac, Propylene glycol, Ammonia, Potassium hydroxide, Iron oxide (E172)

6.2 Incompatibilities
Not relevant.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 25° C.

6.5 Nature and content of packaging
PVC/aluminium blister pack

6.6 Instructions for use, handling and disposal
No special instructions.

7 MARKETING AUTHORISATION HOLDER
Mundipharma AB
Mölndalsvägen 26
412 63 Göteborg

8 AUTHORISATION NUMBERS

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10 DATE OF REVISION OF TEXT
17 June 2003

Exhibit 2

Summary of Product Characteristics

1 NAME OF MEDICINAL PRODUCT

Opidol Uno, 12 mg, 16 mg, 24 mg and 32 mg prolonged release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 prolonged release capsule contains hydromorphone hydrochloride 12 mg, 16 mg, 24 mg and 32 mg corresponding to 10.7 mg, 14.2 mg, 21.4 mg and 28.4 mg hydromorphone, respectively.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard

Opidol Uno 12 mg capsules are rust, opaque capsules marked P-XL 12 mg.
Opidol Uno 16 mg capsules are flesh-coloured opaque capsules marked P-XL 16 mg.
Opidol Uno 24 mg capsules are powder blue, opaque capsules marked P-XL 24 mg.
Opidol Uno 32 mg capsules are white opaque capsules marked P-XL 32 mg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Long-term, severe opioid-sensitive pain, such as cancer pain.

4.2 Posology and method of administration

The capsules should be swallowed whole or the capsules may be opened and the content sprinkled on semisolid food and consumed immediately after. The content of the capsules must not be crushed, chewed or dissolved. Crushed, chewed or dissolved capsules may result in too rapid release and absorption and in that way a life-threatening amount of hydromorphone.

Opioids must be dose-titrated individually because of the wide differences between different patients with regard to pharmacokinetics, intensity and genesis of pain, possible tolerance and age. The therapy is started by titration with a short-acting hydromorphone capsule to a dose of hydromorphine that gives freedom from pain.

Adults: Administered every 24 hours. The dose must be adjusted individually to the condition of the patient, taking into account any previous pain therapy.
12 mg of hydromorphone has an analgesic efficacy equivalent to 90 mg of morphine sulphate given orally.
At break-through pain, short-acting hydromorphone must be used. ~~An opioid naive patient with severe uncontrolled pain must be titrated with immediate release hydromorphone (e.g. Opidol capsules before conversion to Opidol Uno prolonged release capsules). Increasing severity of pain will require increased dosage to achieve the desired relief.~~

Elderly: Dose reduction should be considered.

Children: Not recommended for children aged below 18 years.

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Patients with impaired renal or liver function: As available data on these groups of patients are limited, treatment should begin with the lowest possible dose and the patients must be monitored regularly. Further adjustments to the dose should be made with caution.
The prolonged release capsules may be swallowed whole or divided.

For switching from another peroral or parenteral opioid therapy to Opidol Uno prolonged release capsules the conversion table shown below is used, which is intended to be used as guidelines. The previous daily dose is multiplied by the factor for the opioid used in order to obtain the daily dose of Opidol capsules.

However, a fixed conversion ratio may not be valid for all patients, especially not for patients who are given high doses of opioids. The recommended doses should only be understood as starting points and the patients should be closely followed and frequent titrated (this should read as "frequently titrated") till a satisfactory dose with the new treatment has been achieved.

Opioid	*Peroral*	*Parenteral*
Morphine, acute treatment	0.13	0.8
Morphine, chronic treatment	0.13	0.4
Ketobemidone	0.13	0.4
Methadone	0.4	0.8
Pethidine	0.03	0.11
Hydromorphone	1	
Oxycodone	0.25	

4.3 Contraindications
Respiratory depression with hypoxia or elevated carbon dioxide levels in the blood, paralytic ileus, convulsions, stasis of secretion, coma, acute abdominal pain, seriously impaired liver function, hypersensitivity to hydromorphone or other ingredients in the capsules, anxiety states under the influence of alcohol or hypnotics. Concurrent administration of monoamine oxidase inhibitors or administration within 2 weeks after discontinuation of their use. Use of Opidol Uno prolonged release capsules should be avoided in patients with raised intracranial pressure or head injury.
~~Pre-operative administration of Opidol Uno prolonged release capsules is not recommended~~

4.4 Special warnings and precautions for use
The most serious risk of opioid ~~excess~~ treatment is respiratory depression. Caution should be exercised in pulmonary disease, especially with airflow obstruction (see also section 4.3 "Contra-indications"). ~~As with all narcotics, the drug s~~Should be used with caution in the elderly and ~~infirm~~ patients with reduced general condition, ~~or~~ patients with hypothyroidism, impaired renal or liver function or adrenocortical failure, prostate hypertrophy, Addison's disease, toxic psychosis, delirium tremens, pancreatitis, shock or reduced pulmonary capacity, reduction of the dose should be considered.
Pre-operative administration of Opidol Uno prolonged release capsules is not recommended.
Opidol Uno prolonged release capsules are not either recommended in the first 24 hours post-operatively. After this time they should be used with extreme caution, particularly following abdominal surgery. Opidol Uno prolonged release capsules should not be used if there is a risk of paralytic ileus. Should paralytic ileus be suspected or occur during use, the treatment should be discontinued. Where patients are to undergo cordotomy or other surgical procedure for pain relief, the therapy should be discontinued 24 hours before the operation. If further treatment with Opidol Uno prolonged release capsules is indicated, the dosage should be adjusted to the new post-operative requirement. Drug tolerance may develop in long-term use. Hydromorphone has

a morphine like abuse potential. Treatment with Opidol Uno should be discontinued gradually after long-term use in order to avoid withdrawal symptoms.

4.5 Interactions with other medicinal products and other forms of interaction

Formal interaction studies have not been performed.

Barbiturates like alcohol potentiate the respiratory depression effect of opiates and opioids.

Opidol Uno prolonged release capsules should not be co-administered with monoamine oxidase inhibitors or within two weeks of discontinuation of their use (see section 4.3 "Contra-indications"). Opidol Uno prolonged release capsules potentiate the effects of tranquillisers, anaesthetics, hypnotics and sedatives. If any of these pharmaceuticals are used in combination with Opidol Uno prolonged release capsules, the patient should be watched over, and a reduction of the dose may be necessary.

4.6 Pregnancy and lactation

Pregnancy:

Data from treatment of pregnant women with Opidol is missing. As for other opioids there is a risk of neonatal abstinence at long-term treatment during pregnancy. Opidol must be use during pregnancy solely if the treatment is absolutely necessary.

~~There is no experience of therapy during pregnancy. In animal studies deformities and other embryotoxic effects have been seen at high doses. The clinical relevance of these findings is not known. During pregnancy hydromorphone should be given only on strict indications and when the need of the mother has been weighed against the risks to the child. In the event of long term therapy during pregnancy the risk of neonatal abstinence should be considered.~~

Analgesics of opioid type may cause neonatal respiratory depression. For 2-3 hours before ~~expected~~ delivery ~~hydromorphone~~ Opidol should be given ~~only on strict indications and when the need of the mother has been weighed against the risks to the child~~ with great care.

Animal studies have shown reproduction toxicological effects of hydromorphone (See 5.3). The risk for human is unknown.

Lactation:

Information on ~~The~~ passage of hydromorphone to breast milk ~~has not been studied~~is missing Risk for influence on the baby cannot be excluded. The need of the mother for treatment with Opidol and the advantages of lactation must be weighed against the potential risks to the child.

~~Women should not breastfeed while being treated with hydromorphone.~~

4.7 Effects on ability to drive vehicles and use machines

Treatment with Opidol Uno prolonged release capsules may impair reactive ability. This should be borne in mind when keen attention is required, e.g. when driving.

4.8 Undesirable effects

The commonest side effects are constipation, nausea, vomiting. Constipation may be treated with appropriate laxatives. When nausea and vomiting present a problem, Opidol Uno prolonged release capsules may be combined with antiemetics.

Central Nervous system	
Very common (≥ 10%)	Asthenia, dizziness, somnolence.
Common (≥ 1%)	Confusion, physical dependence, hallucination.
Uncommon (< 1%)	Abuse, agitation, addiction, blurred vision, drowsiness, dysphoria, euphoria, headache, miosis, myoclonus, sedation, seizure.
Vascular	
Common (≥ 1%)	~~Hypotension~~Hypotonia.
Respiratory	
Uncommon (< 1%)	Respiratory depression.
Gastrointestinal	
Very common (≥ 10%)	Constipation, nausea, vomiting.
Common (≥ 1%)	Dry mouth.
Uncommon (< 1%)	Biliary spasm, ileus.
Dermatologic	
Very common (≥ 10%)	Pruritus
Common (≥ 1%)	Rash, sweating.
Uncommon (< 1%)	Urticaria.
Renal and urinary disorders	
Common (≥ 1%)	Urinary retention

Drowsiness usually abates after a few days' administration. Spasms in the bile duct and urinary tract may arise in predisposed individuals. The respiratory-depressive effect is dose-dependent and seldom constitutes a clinical problem.

4.9 Overdosage

Toxicity: Limited experience of overdose. Great individual variations due to development of tolerance.

Symptoms: The symptoms are similar to morphine intoxication with maximum miotic pupils, reduction in consciousness, acute apnoe, respiratory depression, which can be prolonged, hypotension and slow intestinal motor function. At high doses, risk of deep unconsciousness, respiratory stop and circulatory insufficiency may occur.

Treatment: Emptying the stomach and active charcoal. Monitoring of respiration, circulation and degree of consciousness during at least 24 hours. Naloxone reverses the opioid effect but may in opioid tolerant patients induce withdrawal symptoms. At moderate respiratory depression in adults, naloxone 0.04 - 0.4 mg is administered intravenously till the respiratory depression is abolished (the risk of withdrawal symptoms is small with this dose range). At pronounced respiratory depression, initial intravenous administration of naloxone 0.4 mg is carried out and the dose is repeated as required successively till the respiratory depression is abolished. As naloxone has a relatively short duration of action, a practical alternative may be naloxone as continuous infusion (start with 10ug/kg/hour and adjust the dose according to the response). Naloxone cannot replace treatment of respiration in case of serious intoxication. At circulatory insufficiency, liquid is administered intravenously.

Monitor central hemodynamics and at remaining hypotension in spite of adequate filling pressure, dopamine is administered and possibly noradrenaline.
Symptomatic treatment in other respects.~~Indications of overdosage are miosis, respiratory depression and low blood pressure. Circulatory disorders and coma may occur in serious cases.~~
~~Treatment:~~
~~Primary attention should be given to the establishment of clear airways and institution of assisted or controlled ventilation.~~

~~In case of massive overdose, naloxone 0.8 mg is administered intravenously. Repeat at 2-3 minutes intervals as necessary, or by an infusion of 2 mg in 500 mg of normal saline or 5% dextrose (0.004 mg/ml).~~

~~The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Opidol Uno prolonged release capsules will continue to release hydromorphone for up to 12-24 hours after administration. Treatment of the overdose should be adjusted accordingly.~~

~~For less severe overdose, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.~~

~~Naloxone should not be administered in the absence of clinically significant or circulatory depression secondary to morphine overdose.~~

~~Naloxone should be administered cautiously to patients who are known, or suspected, to be physically dependent on hydromorphone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.~~

~~It may be necessary to empty the stomach to remove non absorbed drug, especially in the case of prolonged release capsules.~~

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Narcotic analgesic, ATC-code N02AA03.

Hydromorphone is structurally related with morphine. At analgesic doses hydromorphone and morphine have comparable pharmacological profiles. The analgesic effect is due in part to a changed pain perception and in part to an elevation of the pain threshold. With oral administration the ratio of analgesic potency between hydromorphone and morphine is approximately 7.5:1.
Hydromorphone 12 mg has an analgesic effect equivalent to approx. 90 mg morphine sulphate with peroral administration.
In elderly patients the ~~pain-relieving~~ effects of hydromorphone increases (both with respect to pain relief and adverse reactions). The central nervous system effects of hydromorphone also include respiratory depression, mental symptoms, nausea and vomiting, miosis and release of antidiuretic hormone.
The respiratory-depressive effect of hydromorphone is due in part to an inhibition of the stimulating effect of carbon dioxide on the respiratory centre in the medulla oblongata. This effect may lead to respiratory insufficiency in patients with impaired ability to ventilate as a result of pulmonary disease or the effect of other drugs.

Intoxication with hydromorphone requires respiratory-support therapy and the administration of antidote.
Mental symptoms include euphoria, but also depression, sleeplessness, and disturbances of concentration and memory.

Stimulation of dopamine receptors in the "trigger zone" in the medulla oblongata may give rise to nausea and vomiting. The increased release of anti-diuretic hormone contributes to a reduction in urine volumes during hydromorphone therapy. Hydromorphone increases tone in the smooth muscles of the gastrointestinal canal. This leads to constipation as a result of slower passage of food through the gastrointestinal canal. Pressure in the biliary and urinary ducts also rises, making hydromorphone less appropriate in cases of biliary or urethral spasm.

Hydromorphone has habit-forming characteristics, ~~and t~~Tolerance of the effects of hydromorphone may develop. However this does not usually cause any problems in the treatment of severe pain such as cancer pain.

5.2 Pharmacokinetic properties

Hydromorphone is absorbed from the gastrointestinal canal and undergoes ~~a~~ first-pass metabolism. Average bioavailability is 32%. Hydromorphone is metabolized and excreted in the urine mainly in conjugated form, but also to a smaller amount as unchanged hydromorphone, dihydroisomorphine and dihydromorphine. ~~Opidol Uno Prolonged release capsules give therapeutic plasma levels at administration every 24 hours .~~

~~Studies in healthy volunteers have demonstrated that the administration of Opidol Uno prolonged release capsules result in~~ Maximum plasma hydromorphone concentrations are obtained ~~that attain an initial peak~~ within 2 to 4 hours after dosing of Opidol Uno prolonged release capsules, followed by a ~~broad secondary peak~~/plateau ~~which helps to maintain~~of relatively constant ~~plasma~~ concentrations for at least 24 hours after dosing. At steady state, the ~~availability of hydromorphone from~~ total exposure (AUC) of Opidol Uno prolonged release

capsules over a 24-hour period was equivalent to that provided by immediate release ~~hydromorphone~~Opidol capsules~~,~~ and to Opidol prolonged release capsules given twice daily based on equivalent total daily doses, ~~over a 24-hour period, and but this~~ Opidol Uno ~~was accompanied by~~has lesser fluctuation ~~from the once-a-day preparatio~~of plasma ~~a~~concentrations ~~than both of these~~immediate release Opidol and Opidol prolonged released capsules given twice daily. Sprinkling the contents of the capsule over a soft food had no effect on the plasma profile when compared to Opidol Uno intact capsules, providing an alternative option to patients with difficulty in swallowing.

Studies involving immediate and twice-daily hydromorphone preparations have indicated that the pharmacokinetics are linear across a wide dosage range. ~~Dose proportionality studies involving Opidol Uno prolonged release capsules strengths from 12 mg to 32 mg have confirmed a linearity of pharmacokinetic response.~~ Dosage (form) strength proportionality on a dose-adjusted basis has been demonstrated for three 12 mg capsules to one 32 mg capsule.

A steady state pharmacokinetic study in healthy volunteers has indicated that the once-daily administration of Opidol Uno prolonged release capsule 12 mg provided an availability of hydromorphone equivalent to that of Palladone SR (twice-daily) 6 mg. The Opidol Uno prolonged release capsule 12 mg provided peak and trough concentrations within the range defined by Palladone SR 6 mg bd.

~~A steady state pharmacokinetic study in healthy volunteers has indicated that the once daily administration of Opidol Uno prolonged release capsule 12 mg provided an availability of hydromorphone equivalent to that of Palladone SR (twice daily) 6 mg. The Opidol Uno prolonged release capsule 12 mg provided peak and trough concentrations within the range defined by Palladone SR 6 mg bd.~~

5.3 Preclinical safety data

Like with other opioids hydromorphone causes chromosome aberrations in in-vitro studies. The clinical importance is unknown. No chromosome damaging effects were seen in in-vivo studies. Carcinogenicity of hydromorphone has not been studied.

Studies on pregnagnt animals suggest that hydromorphone has a teratogen potential. If hydromorphone was given during late pregnancy, increased mortality and reduced birth weight of the offspring were seen.~~Hydromorphone is structurally related to morphine and is a metabolite of morphine, codeine and dihydrocodeine. The toxicology of morphine is better known than of hydromorphone. Considering the available data, it is reasonable to conclude that the "risk – benefit" ratio is the same for hydromorphone and morphine in the treatment of chronic severe pain.~~

~~Hydromorphone was non-mutagenic in Ames test and the mouse micronucleus assay.~~

~~Hydromorphone was also non-mutagenic in the mouse lymphoma assay in the absence of exogenous metabolism. A positive response was observed in the mouse lymphoma assay in the presence of exogenous metabolism (S-9) at higher concentrations (≥200 µg/mL). Studies of hydromorphone evaluating the carcinogenic potential have not been conducted.~~

~~There were no treatment-related effects on mating, fertility, or litter parameters (eg, viability, weight, and sex ratio) at doses up to 5 mg/kg/day. The fertility and reproductive no-observable-effect-level (NOEL) of hydromorphone HCl was greater than 5 mg/kg/day (the highest dose tested).~~

~~In animals, no teratogenic effects were noted in rats at doses up to 10 mg/kg, or in rabbits at doses up to 50 mg/kg. Maternal toxicity was observed in both studies. Exposures were at least 1.8 (rat) and 8 (rabbit) times the anticipated human exposure based on AUC from a 32 mg daily oral dose of hydromorphone in humans. However, teratogenic activity with hydromorphone has been reported in the literature with mouse and hamster at oral doses of 5 mg/kg (15 mg/m^2) and 10 mg/kg (118 mg/m^2), respectively, which would be approximately equivalent to 0.7 and 5.5 times a single human oral hydromorphone dose of 32 mg.~~

~~In the perinatal/postnatal study, body weight gain and absolute and relative feed consumption values were reduced in the 2 and 5 mg/kg/day of hydromorphone F_0 groups during the gestation and lactation periods. Peripartum/postpartum pup (F_1) mortality was increased at 2 and 5 mg/kg/day and body weights were reduced during the lactation period. No statistically significant or biologically important differences in fertility, mating, the values for learning, short-term retention, long-term retention, or response inhibition in the F_1 animals at doses as high as 5 mg/kg/day of hydromorphone. The developmental NOEL for the study was 0.5 mg/kg/day of hydromorphone.~~

6 PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Eudragit RS PO; ethylcellulose; silica, stearyl alcohol.

Capsule shell: Gelatin, sodium lauryl sulphate, colloidal anhydrous silica.
Colouring matters:

12 mg capsules:	Titanium dioxide (E171), iron oxide (E172)
16 mg capsules:	Titanium dioxide (E171), iron oxide (E172)
24 mg Capsules:	Titanium dioxide (E171), Indigotin I (E132)
32 mg capsules:	Titanium dioxide (E171)

Ink:
Shellac, Propylene glycol, Ammonia, Potassium hydroxide, Iron oxide (E172)

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and content of packaging

PVC/aluminium blister pack

6.6 Instructions for use, handling and disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Mundipharma AB
Mölndalsvägen 26

412 63 Göteborg

8 AUTHORISATION NUMBERS

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10 DATE OF REVISION OF TEXT

~~30 May 2003~~12.7.2004

Exhibit 3

II. APPLICATION SUMMARY 10

E.3. Subchronic Toxicity/Chronic Toxicity/Carcinogenicity

(see Section V.E.2.)

An extensive literature search revealed no nonclinical subchronic toxicity studies with oxycodone. However, non-GLP range-finding studies in nonpregnant animals (10-12 days of dosing), which were done prior to teratology studies, provide some information on the pharmacotoxic effects of oxycodone hydrochloride.

Rats (n= 2 per dose) given doses of 100, 200, or 300 mg/kg were euthanized in a moribund state following dosing on study day 2. Pharmacotoxic signs included excessive gnawing on the bottom of the cage, rigid body tone, ptosis, exophthalmos, bradypnea, labored breathing, excessive lacrimation, hypothermia, decreased activity, and tremors. Necropsy of these animals revealed bloody fluid and mucosal hemorrhages in the urinary bladders.

Dose and time-related pharmacotoxic signs were evident in rats dosed with 5 or 50 mg/kg of oxycodone hydrochloride. The 5 mg/kg group displayed stereotyped behavior (excessive gnawing on the bottom of the cage), increased activity, and excessive gnawing on the forelimbs. Pharmacotoxic signs seen in the 50 mg/kg included stereotyped behavior, increased/decreased activity, excessive gnawing on the

forelimbs, rigid body tone, bradypnea, labored breathing, excessive lacrimation, evidence of chromodacryorrhea, fecal and urine staining.

A number of the pharmacotoxic signs found are typical of opioid overdosing in animals. These include stereotypy, rigid posture, increases/decreases in motor activity, hypothermia, depressed respiration, tremors, and urinary bladder changes.

In a preliminary 12 day study in rabbits (n= 1/dose), no drug-related toxic effects were discernable at 5 mg/kg. Doses of 25, 75, and 150 mg/kg were associated with variable and transient pharmacotoxic signs which are typical of high dose opioid treatment in animals. These included decreased activity (25 and 150 mg/kg), decreased or absent defecation (75 and 150 mg/kg), and convulsions (on one occasion at 25 mg/kg). The animal given 300 mg/kg died after the 5th dose. Antemortem signs were also indicative of opioid overdosage and included decreased activity, dilated pupils, prostration, decreased defecation, and weight loss well beyond that of concurrent control changes. The animal convulsed just prior to death.

A literature search revealed no published reports regarding either the nonclinical chronic toxicity or carcinogenicity of oxycodone.

Exhibit 4

COMPANY CORE DATA SHEET

OXYCODONE HYDROCHLORIDE

This Company Core Data Sheet is a summary of relevant core information on this/these product/s. It should be used when Summary of Product Characteristics or other Product Documents are being prepared, or when information regarding this product is being updated. However, details in some sections (indications, dosage, etc.) may differ from country to country, and each national product information document should always be kept in line with the marketing authorization granted by the local regulatory authority. In addition, under the Pharmaceutical Properties section, details of pharmaceutical features should be checked against the pharmaceutical section of the registration file. The Company Core Safety Information is located in Sections 4.3 to 4.9.

Country Responsible

United States of America

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Date and Issue Number

~~Date: 24 April 2002~~
Date: 19 Aug 2003

Version No. 01
~~FINAL~~
DRAFT

Revision of April 24 2002

Robert F. Reder, M.D. Date

1. NAME OF THE MEDICINAL PRODUCT

Trademark
Please refer to local labeling.

Generic (INN) Name
Oxycodone Hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Please refer to local labeling.

3. PHARMACEUTICAL FORM

Please refer to local labeling.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indication

Pain requiring the use of an opioid analgesic.
Please refer to local labeling.

4.2. Posology and Method of Administration

4.2.1. General

Controlled-release (prolonged-release, extended-release) tablets:

~~*Oral – Adults*~~
~~Recommended every 12 hours. The dose level must be tailored to the individual patient based on his/her condition and taking into consideration any prior pain therapy. Normal initial dose for patients who have not previously been treated with opioids: 10 mg every 12 hours.~~

~~Oxycodone HCL controlled-release tablets must be swallowed whole. They must not be broken, chewed or crushed.~~

~~*Oral – Children*~~
~~Experience with oxycodone hydrochloride in children is limited and its use has not been fully evaluated in clinical studies. No dose recommendations can be made.~~

Immediate release tablets, capsules and oral liquids:

~~*Oral – Adults*~~
~~Dosage should be adjusted to the severity of the pain and the response of the patient. The usual adult dosage is 5mg of oxycodone HCl every 4-6 hours as needed for pain.~~

~~*Oral – Children*~~
~~Experience with oxycodone hydrochloride in children is limited and its use has not been fully evaluated in clinical studies. No dose recommendations can be made.~~

~~*Parenteral – Adults*~~Please refer to local labeling.

Parenteral
Please refer to local labeling.

4.3. Contraindications

Oxycodone is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated: severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, severe respiratory depression with hypoxia, elevated carbon dioxide levels in the blood, or paralytic ~~ileus.~~
ileus.[1]

4.4. Special Warnings and Precautions for Use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly or infirm; patients with severely impaired pulmonary, hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, alcoholism, delirium tremens, pancreatitis, hypotension, head injury (due to risk of increased intracranial pressure) or patients taking MAO inhibitors.[2]

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain ~~control. The patient may develop physical dependence, in which case an abstinence syndrome may be seen following abrupt cessation.~~
control.[3] Prolonged use of this product [preparation] may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, doses should be tapered gradually to prevent signs and symptoms of withdrawal in a patient who may be physically dependent.

Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. The controlled

release tablets must~~not~~ be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled ~~crushed, as this may lead to an overdose~~ release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone. (see section 4.9).[4]

The product [preparation] should be used with great care, particularly in patients with a history or alcohol and drug abuse. The development of psychological dependence [addiction] to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of psychological dependence [addiction] in chronic pain patients.[5,6,7,8,9]

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

4.5. Drug Interactions

There can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as alcohol, other opioids, sedatives, hypnotics, anti-depressants, sleeping aids, phenothiazines and neuroleptic drugs, etc.[NOTEREF _Ref36971650 \f \h]

Oxycodone is metabolized in part via the CYP2D6 and CYP3A4 pathways. While these pathways may be blocked by a variety of drugs, such blockade has not yet been shown to be of clinical significance with this agent.[10]

4.6. Pregnancy and Lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.[11]

The drug penetrates the placenta and can be found in breast milk.[12] [NOTEREF _Ref36970974 \f \h]

4.7. Effects on Ability to Drive and Use Machines

Oxycodone may impair the ability to drive and use machines.

4.8. Undesirable Effects

The adverse experiences listed below are classified by body system according to their incidence (common or uncommon). Common adverse drug experiences have an incidence of ≥ 1% and uncommon adverse drug experiences have an incidence of < 1% [13]

Gastrointestinal

~~*Common*~~	~~abdominal pain~~ ~~anorexia~~ ~~constipation~~ ~~diarrhea~~ ~~dry mouth~~ ~~dyspepsia~~ ~~nausea~~ ~~vomiting~~
Common	abdominal pain[14] anorexia[NOTEREF _Ref36966591 \f \h] constipation[NOTEREF _Ref36966591 \f \h] diarrhea[NOTEREF _Ref36966591 \f \h] dry mouth[NOTEREF _Ref36966591 \f \h] dyspepsia[NOTEREF _Ref36966591 \f \h] nausea[NOTEREF _Ref36966591 \f \h] vomiting[NOTEREF _Ref36966591 \f \h]
~~*Uncommon*~~	~~biliary pain~~ ~~dysphagia~~ ~~eructation~~ ~~flatulence~~ ~~gastrointestinal disorders~~ ~~ileus~~ ~~taste perversion~~
Uncommon	biliary pain[15, 16, 17] dysphagia[18] eructation[NOTEREF _Ref36966813 \f \h] flatulence[NOTEREF _Ref36966813 \f \h] gastrointestinal disorders[19] ileus[20] taste perversion[21, 22]

Central Nervous System

~~*Common*~~	~~anxiety~~ ~~asthenia~~ ~~confusion~~ ~~dizziness~~ ~~headache~~ ~~insomnia~~ ~~nervousness~~

	~~somnolence~~
	~~thought abnormalities~~
Common	anxiety[NOTEREF _Ref36967756 \f \h]
	asthenia[NOTEREF _Ref36966591 \f \h]
	confusion[NOTEREF _Ref36967756 \f \h]
	dizziness[NOTEREF _Ref36967877 \f \h]
	headache[NOTEREF _Ref36966591 \f \h]
	insomnia[23]
	nervousness[NOTEREF _Ref36967877 \f \h]
	somnolence[NOTEREF _Ref36967984 \f \h]
	thought abnormalities[24]
~~*Uncommon*~~	~~agitation~~
	~~amnesia~~
	~~convulsions~~
	~~depression~~
	~~emotional lability~~
	~~euphoria~~
	~~hallucinations~~
	~~hypertonia~~
	~~hypesthesia~~
	~~hypotonia~~
	~~malaise~~
Uncommon	agitation[NOTEREF _Ref36967756 \f \h]
	amnesia[25]
	convulsions[26, 27]
	depression[28]
	emotional lability[NOTEREF _Ref36967877 \f \h]
	euphoria[NOTEREF _Ref36967877 \f \h]
	hallucinations[NOTEREF _Ref36967877 \f \h]
	hypertonia[NOTEREF _Ref36967877 \f \h]
	hypesthesia[NOTEREF _Ref36967877 \f \h]
	hypotonia[NOTEREF _Ref36967877 \f \h]
	malaise[NOTEREF _Ref36967877 \f \h]
Uncommon (continued)	
	~~muscle contractions involuntary~~
	~~paresthesia~~
	~~speech disorder~~
	~~tremor~~
	~~vertigo~~
	~~vision abnormalities~~
	~~withdrawal syndrome~~
	muscle contractions involuntary[NOTEREF _Ref36967984 \f \h]
	paresthesia[29]
	speech disorder[NOTEREF _Ref36967984 \f \h]

	tremor[NOTEREF _Ref36967984 \f \h] vertigo[NOTEREF _Ref36967984 \f \h] vision abnormalities[NOTEREF _Ref36969113 \f \h] withdrawal syndrome[NOTEREF _Ref36967984 \f \h]
Genitourinary	
~~*Uncommon*~~	~~amenorrhea~~ ~~decreased libido~~ ~~impotence~~ ~~urinary retention~~
Uncommon	amenorrhea[30] decreased libido[31] impotence[NOTEREF _Ref36972561 \f \h] urinary retention[32]
Cardiovascular	
~~*Common*~~	~~orthostatic hypotension~~
Common	orthostatic hypotension[33]
~~*Uncommon*~~	~~hypotension~~ ~~palpitations~~ ~~supraventricular tachycardia~~ ~~syncope~~ ~~vasodilation~~
Uncommon	hypotension [34] palpitations[35] syncope[NOTEREF _Ref36968441 \f \h] vasodilation[NOTEREF _Ref36968441 \f \h]
Metabolic and Nutritional	
~~*Uncommon*~~	~~dehydration~~ ~~edema~~ ~~peripheral edema~~ ~~thirst~~
Uncommon	dehydration[36] edema[NOTEREF _Ref36968482 \f \h] peripheral edema[NOTEREF _Ref36968482 \f \h] thirst[NOTEREF _Ref36968482 \f \h]
Respiratory	
~~*Common*~~	~~bronchospasm~~ ~~cough decreased~~ ~~dyspnoea~~
Common	cough decreased[37]

	dyspnoea[38]
~~*Uncommon*~~	~~respiratory depression~~
Uncommon	respiratory depression[NOTEREF _Ref36969223 \f \h]

Dermatological

~~*Common*~~	~~rash~~
Common	rash[39]
~~*Uncommon*~~	~~dry skin~~
	~~urticaria~~
Uncommon	dry skin[NOTEREF _Ref36969113 \f \h]
	urticaria[40, 41]

General

~~*Common*~~	~~chills~~
	~~pruritus~~
	~~sweating~~
Common	chills[NOTEREF _Ref36966591 \f \h]
	pruritus[NOTEREF _Ref36969113 \f \h]
	sweating[NOTEREF _Ref36969113 \f \h]
~~*Uncommon*~~	~~allergic reaction~~
	~~drug dependence~~
	~~miosis~~
	~~tolerance~~
Uncommon	allergic reaction[42]
	anaphylaxis[43]
	drug dependence[44]
	miosis[45]
	tolerance[46]

4.9. Overdosage

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence, progressing to stupor or coma, skeletal muscle flaccidity, miotic pupils, bradycardia, hypotension, and death.

A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.[NOTEREF _Ref36971650 \f \h]

5. PHARMACOLOGICAL INFORMATION

5.1. Pharmacodynamic Properties

Oxycodone HCl is an opioid agonist with no antagonistic action. Its effects are similar to those of morphine.[NOTEREF _Ref36971650 \f \h]

The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative. The mechanism of action involves CNS opioids receptors for endogenous compounds with opioid-like activity.[NOTEREF _Ref36971650 \f \h]

5.2. Pharmacokinetic Properties

Oxycodone controlled-release tablets release oxycodone more slowly than immediate-release oxycodone tablets or capsules. Release in vitro is pH-independent.[47]

The controlled-release tablets exhibit a two-phase absorption pattern with apparent absorption half-times of 0.6 and 6.9 hours. Peak plasma concentration is attained after three hours. The plasma elimination half-life is approximately 4.5 hours. Food intake has little or no effect on the absorption of oxycodone from controlled-release tablets.[48]

Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein.[49]

Oxycodone is metabolized in the liver to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. CYP3A4 and CYP2D6 being the primary enzymes responsible for the formation of noroxycodone, oxymorphone and noroxymorphone. The in vitro drug-drug interaction studies with noroxymorphone using human liver microsomes resulted in no significant inhibition of CYP2D6 and CYP3A4 activities, which suggest that noroxymorphone may not alter the metabolism of other drugs that are metabolized by CYP2D6 and CYP3A4.[50] Noroxymorphone has been shown to bind to μ-opioid receptor.[51] Although ~~various conjugated glucuronides. Oxymorphone and noroxycodone are produced via a cytochrome P450 dependent enzyme system. The~~oxymorphone has been shown to be active, the analgesic effects of the metabolites are thought to be clinically insignificant.[NOTEREF _Ref36973839 \h * MERGEFORMAT]

The active drug and its metabolites are excreted in both urine and feces.[NOTEREF _Ref36971650 \f \h]
The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.[NOTEREF _Ref36973768 \f \h]

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.[NOTEREF _Ref36973768 \f \h]

~~The drug penetrates the placenta and can be found in the breast milk.~~

When compared to normal subjects, patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone, and lower plasma concentrations of oxymorphone. There may be an increase in the elimination half-life of oxycodone, and this may be accompanied by an increase in drug effects.[52]

When compared to normal subjects, patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) may have higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-life of oxycodone, and this may be accompanied by an increase in drug effects. [53]

5.3. Preclinical Safety Information

5.3.1. Teratogenicity

The effect of oxycodone in human reproduction has not been adequately studied. No studies on fertility or the post-natal effects of intrauterine exposure have been carried out. However, studies in rats and rabbits with oral doses of oxycodone equivalent to 3 and 47 times an adult human dose of 160 mg/day respectively, did not reveal evidence of harm to the fetus due to oxycodone.[54]

5.3.2. Carcinogenicity

No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.

5.3.3. Mutagenicity

Data from several studies indicate that the genotoxic risk of oxycodone to humans may be considered low. Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses of up to 5000 μg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) at doses of up to 1500 μg/ml, and with activation after 48 hours of exposure at doses up to 5000 μg/ml, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 μg/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 μg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 μg/ml or greater with metabolic activation and at 400 μg/ml or greater without metabolic activation.[55]

6. PHARMACEUTICAL INFORMATION

6.1. Constituents

Please refer to local labeling.

6.2. Incompatibilities

Parenteral Dosage Form

Please refer to local labeling

6.3. Shelf Life

Please refer to local labeling.

6.4. Special Storage Conditions

Please refer to local labeling.

6.5. Packaging

Please refer to local labeling.

6.6. Instructions for use/handling

Please refer to local labeling.

Formatted: Bullets and Numbering

7. NAME OR STYLE AND PERMANENT ADDRESS OR REGISTERED PLACE OF BUSINESS OF THE HOLDER OF THE MARKETING AUTHORIZATION

Please refer to local labeling.

8. MARKETING AUTHORIZATION NUMBERS

Please refer to local labeling.

9. DATE OF APPROVAL/REVISION

Please refer to local labeling.

10. DATE OF APPROVAL/REVISION OF THE CCDS

~~24 April 2002~~REFERENCES

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[21] Central Repository Stamford, CT Vol 105, p. 165
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Human Chromosomal Aberration Test: DSE-151-GLP.
Mouse Lymphoma Assay: DSE-150-GLP.

Exhibit 5

To: Grace, John[/O=PURDUE/OU=UKCAM/CN=RECIPIENTS/CN=TECHNICAL SERVICES/CN=JSG01]
Cc: O'Connell, Cathleen[/O=PURDUE/OU=PURDUE US/CN=RECIPIENTS/CN=OCONNELC]; Garner, Steve[/O=PURDUE/OU=UKCAM/CN=RECIPIENTS/CN=REGISTRATION/CN=SGA01]; Haspineall, John[/O=PURDUE/OU=UKCAM/CN=RECIPIENTS/CN=REGISTRATION/CN=JRH01]; Reder, Robert[/O=PURDUE/OU=PURDUE US/CN=RECIPIENTS/CN=REDERR]
From: Smilde, Nienke
Sent: Thur 10/2/2003 8:32:33 AM
Subject: RE: Draft Revised Oxycodone CCDS

Dear John,

Please find enclosed my comments to the revised Oxycodone CCDS, (as I wasn't sure whether you would collect all of the eruopean comments first I have cc-ed dr Reder and Cathleen)

1) section 4.8: the frequencies of ADR's of more or less than 1% should be more detailed according to the european guideline for SPC's from 1999. It should include
* **more than 10%**
* **10- 1%**
* **1 - 0.1%**
* **0.1 - 0.01%**
* **less than 0.01%**

Our authorities take these guidelines very strict. From a commercial point of view it is also very important to distinguish between more than 10% (very common) and more than 1% (common), otherwise all the common ones are also classified as very common ones.

2) references: internal papers might not be accepted as a reference to substantiate the inclusion of a certain ADR, except if it refers to a certain PSUR. I'm not sure what 'Central Repository Stamford' means, but please note that we have to submit all these documents to change the labelling. We also need a clinical expert report.

3) other sections than safety sections, e.g. pharmacokinetics: The information included in these sections cannot be changed that easily and has often be agreed after long discussion with the authorities, so I trust that I do have to change this ! Furthermore our authorities have repeatedly asked us to show more compliance with Vol 9 and ICH E2C in our PSURs, for example by inlcuding only information in the CDS which is labelled in all countries. It might be an idea to create a Core Safety Data Sheet (CSDS) which could be included in a PSUR, instead of a CDS.

I hope these comments are useful,
best regards, Nienke

-----Original Message-----
From: O'Connell, Cathleen
Sent: woensdag 1 oktober 2003 19:55
To: Haspineall, John; Grace, John; Lloyd, Sarah; Santopolo, Anthony; Hargreaves, Dr. Ronald
Cc: WWRA Country Heads; Croswell, Roger; Reder, Robert; Russell, Clare; Champion, Julia; Frimmel, Agi; Maniglia, Charles; Negron, Isabel; Storey, Lee Ann; Velazquez, Maria; White, Stephanie
Subject: Draft Revised Oxycodone CCDS
Importance: High

Attached is the draft revised core data sheet for oxycodone, with annotations. Because of the pressing issues related to the upcoming PSUR and various SPCs, etc., we would like any and all comments your groups have on the proposed changes by Monday, 6 October. (Dr. Reder would like to wrap this up by early next week, so he can issue the final CCDS.) Note that references are being compiled, (they weigh 75 pounds and are in 9 volumes) and are being shipped this week to M. Ermini, E. Sharrah, C. McDonald, and T. Zimmerman.

Given the tight time frame for your review and comment I have copied all WWRA Country Heads directly. Please work with your Regional Regulatory Head to provide comments, sending them directly to Dr. Reder, copying myself and Dr. Lucille Russell. (You should already have had a chance to review the changes to section 4.4. Note that any comments you may have already sent will be considered, although timing did not allow them to be addressed prior to release of this draft for full review.)

Also attached is the "MedDRA map" (WhoART terms mapped to MedDRA terms) that will be incorporated as an appendix in the revised core data sheet.

Thank you.

<< File: oxy MedDRA map.rtf >>

<< File: Oxy CCDS 26 Sept 03 redline.doc >>

Exhibit 6

From: Udell, Howard
Sent: Thursday, June 08, 2000 6:08 PM
To: Sackler, Dr Richard; Goldenheim, Paul; Friedman, Michael
Cc: hru; Croswell, Roger; sdb; Sackler, Dr Mortimer; Manners, Paul
Subject: RE: OxyContin - France

CONFIDENTIAL ATTORNEY-CLIENT COMMUNICATION

All -

Thank you for copying me Richard. Stuart discussed this with me this evening. I'm getting into this exchange a bit late, but I think that the most offensive part of the latest proposal is the beginning of the first sentence. Would we have a chance of convincing them to leave out the words I've highlighted?

> **Current (7 June) French Revised Proposal**
> When selecting an opioid, the prescriber must take into account the fact that in *in vitro* genotoxicity studies, the mutagenic potential of oxycodone appeared at lower doses than in the case of other opioids. ~~Currently available data do not preclude a mutagenic risk *in vivo*., but it was not mutagenic *in vivo* (mouse micronucleus assay) even at toxic doses. specifically~~ In one test performed *in vivo* (mouse micronucleus assay), oxycodone did not appear mutagenic.

I would argue that the use of this language gives undue emphasis to this insignificant in vitro data and dilutes (by its absence anywhere else in the PI) the more serious factors a physician must "take into account" when considering the use of the drug.

I would like to participate in tomorrow's conference call.

Howard R. Udell
(203) 854-7020
hudell@pharma.com

-----Original Message-----
From: **Sackler, Dr Richard**
Sent: Thursday, June 08, 2000 8:22 AM
To: Goldenheim, Paul; Friedman, Michael
Cc: hru; Croswell, Roger
Subject: RE: OxyContin - France

Please ask Ian what his next wording change would be that he hopes would be accepted. I still don't love this. By separating sentences, we have lost something. And the emphasis on one study is disappointing too.

Richard S. Sackler, M.D.
President, Purdue Pharma
Telephone 203 854 **7100**
Internet rss@pharma.com

Intranet http://library.pharma.com/directory/TelephoneNumber.asp?as_tel=7100&B1=Search
Local Time 6/8/00 8:17:25 Connecticut

-----Original Message-----
From: Goldenheim, Paul
Sent: Thursday, June 08, 2000 7:35 AM
To: Sackler, Dr Richard; Friedman, Michael
Cc: hru; Croswell, Roger
Subject: RE: OxyContin - France

Funny, I think I am even less comfortable than the two of you, but maybe I'm wrong.

Richard, I also was thinking about going another round. What would you suggest for a specific wording recommendation?

paul.goldenheim@pharma.com

-----Original Message-----
From: Sackler, Dr Richard
Sent: Thursday, June 08, 2000 12:03 AM
To: Friedman, Michael
Cc: pdg; hru
Subject: RE: OxyContin - France

I think that we are 80% there. But I think we could do better if we went one more round.
The comparative statement is still a separate sentence which Janssen or others might lift out of context.

Richard S. Sackler, M.D.
President, Purdue Pharma
Telephone 203 854 **7100**
Internet rss@pharma.com
Intranet http://library.pharma.com/directory/TelephoneNumber.asp?as_tel=7100&B1=Search
Local Time 6/7/00 11:55:36 Connecticut

-----Original Message-----
From: Friedman, Michael
Sent: Wednesday, June 07, 2000 11:15 PM
To: rss
Subject: FW: OxyContin - France
Importance: High

I am comfortable with this. How about you?
Michael Friedman
friedman@pharma.com
(203) 854 7290

-----Original Message-----
From: Croswell, Roger
Sent: Wednesday, June 07, 2000 8:14 AM
To: Sackler, Dr Richard; Goldenheim, Paul; Friedman, Michael
Cc: Claydon, Ian; Garner, Steve

Subject: FW: OxyContin - France
Importance: High

Dear Richard, Paul and Michael,

According to Steve Garner's latest e-mail (reproduced below) on the French OxyContin situation I think you will agree they have made significant progress in negotiating with the French.

As Richard and Paul requested I am showing below the evolution of the text on the mutagenicity issue. It is advisable for us to try and reach closure on this issue as soon as possible. It is probably the best that can be achieved and still permit us to obtain the marketing authorization. Please note, Ian, Steve, Andre and Mortimer all believe we should accept the current French proposal. I also support this action. **Please provide your thoughts about accepting this most current French proposal direct to Ian Claydon as soon as possible.**

Original Proposal from France

When selecting an opioid, the prescriber must take into account the fact that in *in vitro* genotoxicity studies, the mutagenic potential of oxycodone appeared at lower doses than in the case of other opioids. Currently available data do not preclude a mutagenic risk *in vivo*.

Revised Proposal from France

When selecting an opioid, the prescriber must take into account the fact that in *in vitro* genotoxicity studies, the mutagenic potential of oxycodone appeared at lower doses than in the case of other opioids. ~~Currently available data do not preclude a mutagenic risk *in vivo*.~~

Most Recent Napp Reproposal

When selecting an opioid, the prescriber must take into account the fact that in *in vitro* genotoxicity studies,

the mutagenic potential of oxycodone appeared at lower doses than in the case of other opioids. ~~Currently available data do not preclude a mutagenic risk *in vivo*~~., but it was not mutagenic *in vivo* (mouse micronucleus assay) even at toxic doses.

Current (7 June) French Revised Proposal

When selecting an opioid, the prescriber must take into account the fact that in *in vitro* genotoxicity studies, the mutagenic potential of oxycodone appeared at lower doses than in the case of other opioids. ~~Currently available data do not preclude a mutagenic risk *in vivo*., but it was not mutagenic *in vivo* (mouse micronucleus assay) even at toxic doses. specifically~~ In one test performed *in vivo* (mouse micronucleus assay), oxycodone did not appear mutagenic.

Regards,

Roger
roger.croswell@pharma.com
VP WWRA Purdue Pharma LP
Tel: (203) 854-7260
Fax: (203) 851-5229
Cellular: (203) 984-5102

-----Original Message-----

From:	**Garner, Steve**
Sent:	Wednesday, June 07, 2000 4:18 AM
To:	Sackler, Dr Richard; Sackler, Dr Mortimer; Goldenheim, Paul; Friedman, Michael
Cc:	Manners, Paul; Miller, Dr Allan; Claydon, Ian; Croswell, Roger; Andre Abric (E-mail); Bashforth, Simon
Subject:	OxyContin - France

Dear all,
The French Agency has responded to our last letter in which we suggested alternative text regarding the mutagenic potential of oxycodone.
You will recall that we suggested the addition of the wording that oxycodone "*was not mutagenic in vivo (mouse micronucleus*

assay) even at toxic doses".

The Agency has said that they will accept something very similar, specifically
"In one test performed in vivo (mouse micronucleus assay), oxycodone did not appear mutagenic."

If we agree, the Agency has confirmed that the Marketing Authorisations will be issued.

Please can you advise whether you are willing to accept their proposal.

Best regards

Steve
Ext. 2322
International Regulatory Affairs
Int. R & D (UK)

Exhibit 7

In response to inquiries of some of its customers and the FDA, Mallinkrodt has indicated its intention to conduct genotoxicity testing of representative Î±, Î²-unsaturated ketone impurities from some of their opioid products. Mallinkrodt's objective in the testing is to provide a genotoxicity database that will address FDA's and their customers' concerns regarding the potential genotoxicity of this class of opioid impurities. Mallinkrodt understands that Purdue Pharma plans to perform genotoxicity testing of morphinone and has inquired as to Purdue Pharma's interest in sharing the results of the genotoxicity studies with morphinone and in providing toxicological consultation in regard to their genotox testing program. In return, Mallinkrodt would provide a supply of morphinone without charge and may provide the results from their testing program. Phil Goliber and I request non-objection to initiating more detailed discussions with Mallinkrodt to develop the potential scope and limitations of any such interaction and to evaluate the potential benefit in this interaction. Depending on the outcome of these discussions, Phil and I may request formalization of a joint interaction with Mallinkrodt in this matter. Under the right circumstances, there may be benefit to our product line and development pipeline in this interaction. In this regard, 1. Purdue Pharma should play a pivotal role in selection of the Î±, Î²- unsaturated ketone impurities to be tested 2. Purdue Pharma should play a pivotal role in the selection and oversight of the specific genotoxicity studies performed and the CRO that performs the work 3. the The reports and data from the joint studies should be directly submitable by Purdue Pharma to regulatory agencies. Potential benefits that could be derived as a consequence of the interaction are: 4. Aaccessibility to Î±, Î²-unsaturated ketone impurities in opioids of interest to Purdue Pharma (i.e., oxycodone, hydromorphone, naloxone, and/or naltrexone) 5. Aassurance that Î±, Î²-unsaturated ketone impurities in opioids of interest to Purdue Pharma are tested in a scientifically reliable fashion and that the results are valid 6. Aadvance knowledge of genotoxicity study results for the Î±, Î²- unsaturated ketone impurities in opioids of interest to Purdue Pharma which will allow us to prepare appropriate regulatory, manufacturing, and, if necessary, additional testing strategies to address potential issues 7. Llower cost of testing than if Purdue Pharma, alone sponsored the work. The primary downside of a joint interaction is the unbudgeted resource consumption (toxicological, analytical, management time and testing). Potential negatives in not creating a joint interaction are: 8. Mallinkrodt will likely test morphinone themselves; this would pose the potential for Mallinkrodt's results to contradict our study results (likelihood of this is unknown) 9. Iinaccessibility to potentially important genotoxicity results on Î±, Î²-unsaturated ketone impurities in opioids of interest to Purdue Pharma (the FDA will have the information, we won't) 10. Llack of control over the technical quality of Mallinkrodt's testing program and test results (it is not clear that Mallinkrodt possesses a strong internal toxicological resource) 11. Iinitiation of possibly unnecessarily duplicative genotox testing to support product lines or development programs (e.g., oxycodone)

Exhibit 8

```
Table for FDA Responses - Rhodes (S-033) and Noramco (S-038)
(Manufacturers of API)     Updated as of 6Feb 2004  |Q#|Mf|FDA
Comments                    |Action Item                      |Resp  |
Target|Date |Comments/Status          | |  |r |
|                                  |       |Date  |      |
| |GENERAL
| |DS Characterization
| |1e|N |To ensure the consistency of|Need to know how we can
establish|RO/ PP|13Feb |     |(Via finalized (OK with P| |  |  |the
physical nature of the  |equivalence of materials from all|      |
|     |Bullock's group), signed | |  |  |drug substance obtained from|
mfrs. (Comparison of physical    |(SS to|       |      |off, QA'd
report)        | |  |  |various vendors, provide a  |state of T2 to
|assist|       |      |                          | |  |  |specification
for the       |Noramco/Mallinckrodt API.)       |with  |       |      |
At 3Feb meeting, PP      | |  |  |morphic form of xycodone HCl|
|DP    |       |      |provided SSNMR and XRPD  | |  |  |using
techniques such as    |Provide Comparison report        |issues|
|     |data to show that        | |  |  |PXRD, DSC, FTIR, etc.       |
(Pharmaceutical analysis report  |)      |       |      |differences
among        | |  |  |Alternatively, provide data |with SSNR,
Solubility XRPD etc)  |       |       |      |Mallinckrodt batches used|
|  |  |supporting that the         |                               |
|       |      |in BE for Wilson approval| |  |  |variability in the
morphic  |                                 |       |       |      |had no
impact on BE.     | |  |  |form of the drug substance  |
|       |       |      |                          | |  |  |does not impact
on the drug |                                 |       |       |      |At
3Feb meeting, RO      | |  |  |product performance such a  |
|       |       |      |provided data to support | |  |  |drug substance
aggregation, |                                 |       |       |      |
that differences in DS   | |  |  |blend uniformity,           |
|       |       |      |from Mallinckrodt, Rhodes| |  |  |dissolution,
and            |                                 |       |       |      |
and Noramco are not      | |  |  |bioavailability.           |
|       |       |      |apparent in the DP.      | |  |  |
|Generate new data on solubility  |RO    |13Feb |      |
| |  |  |                            |-Titration and buffer experiment
|       |       |      |                          | |  |  |
|to show results after equilibrium|      |       |      |
| |  |  |                            |
|       |       |      |                          | |  |  |
|Sample Wilson API to complete    |PP    |06Feb |      |
| |  |  |                            |testing
|       |       |      |                          | |  |  |
|Comments to SS (for 1d and 1e)   |Team  |       |      |
| |  |  |                            |Final response to team
|SS    |13Feb |      |                          | |  |  |
|Need to be consistent with       |RO    |TBD   |      |Need to do this
before we| |  |  |                            |verbiage to describe
```

```
"morphic    |      |      |     |finalize our internal    | |  |  |
|form" to FDA Consensus within    |      |      |     |reports.  Do
not want    | |  |  |                             |Company as to
verbiage  for      |      |      |     |conflicting language sent| |
|  |                          |morphic forms                  |
|     |     |to FDA.                   | |  |  |
|.  Meet with vendors            |CL/RO |TBD   |     |
| |  |  |                         |(Mallinckrodt and Noramco) to
get|      |      |     |                           | |  |  |
|buy-in for our verbiage.        |      |      |     |
| |1a|R |The data indicate that the  |Provide Equivalency report
|RO/   |      |     |(Via finalized (OK with P| |  |  |morphic form of
the drug    |(Pharmaceutical analysis report  |PP/ SS|18Feb |     |
Bullock's group), signed | |  |  |substance obtained from     |with
SSNR, Solubility XRPD etc)  |      |(draft|     |off, QA'd report)
| |  |  |Rhodes (and Noramco) is a   |
|     |)     |     |                         | |  |  |monohydrate of
oxycodone    |                                 |      |27Feb |     |PP
and RO provided data  | |  |  |hydrochloride; the batch    |
|     |(final|     |at 3Feb meeting to       | |  |  |data provided
for moisture  |                                 |      |)     |     |
support that differences | |  |  |content of three batches of |
|     |      |     |in DS from Mallinckrodt, | |  |  |drug substance
supplied by  |                                 |      |      |     |
Rhodes and Noramco are   | |  |  |Rhodes were 5.1%, 4.8%, and |
|     |      |     |not apparent in the DP.  | |  |  |5.1%. Oxycodone
|                                |      |      |     |
| |  |  |hydrochloride monohydrate   |
|     |      |     |                         | |  |  |has calculated
water content|                                 |      |      |     |
| |  |  |of 4.9%. In addition, the   |
|     |      |     |                         | |  |  |preponderance
of data       |                                 |      |      |     |
| |  |  |provided (differential      |
|     |      |     |                         | |  |  |scanning
calorimetry,       |                                |      |      |
|                         | |  |  |melting point, and XRPD)    |
|     |      |     |                         | |  |  |suggest that
the drug       |                                 |      |      |     |
| |  |  |substance from Rhodes may be|
|     |      |     |                         | |  |  |a different
polymorph than  |                                 |      |      |
|                         | |  |  |that from Noramco. If these |
|     |      |     |                         | |  |  |data are
incorrect, please  |                                |      |      |
|                         | |  |  |provide clarification.      |
|     |      |     |                         | |  |  |
|Need clarification from FDA (on  |RO/ JK|TBD   |     |JK-FDA stated
we can fax | |  |  |                            |melting point and
"any"          |      |      |     |questions                 | |  |  |
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|information within organization) |      |      |     |
| |  |  |                          |
|     |     |     |                      | |  |  |
|Send questions to JK for FDA     |Team  |03Feb |     |
| |  |  |                          |Rhodes to mfr 3 API validation
|RS    |01Jul |     |                      | |  |  |
|batches                          |      |      |     |
| |  |  |                          |Wilson to receive API
|KS    |01Jul |     |                      | |  |  |
|Manufacture DP in Wilson         |SS/KS |15Jul |     |
| |  |  |                          |Perform release testing
|KS    |30Jul |     |                      | |  |  |
|Put DP batches on stability      |KS    |30Jul |     |
| |  |  |                          |Perform validation testing
|KS/JL |15Aug |     |                      | |1b|R |The drug
substance obtained |                              |RO/PP |13Feb |
|                        | |  |  |from Mallinckrodt cannot be |
|     |     |     |                      | |  |  |a monohydrate
since the     |                                |      |      |     |
| |  |  |water content is too low.   |
|     |     |     |                      | |  |  |The
Mallinckrodt drug      |                                |      |
|     |                        | |  |  |substance differs from the  |
|     |     |     |                      | |  |  |Rhodes drug
substance in    |                                |      |      |
|                        | |  |  |XRPD pattern as well. Please|
|     |     |     |                      | |  |  |provide
clarification.     |                                |      |      |
|                        | |2 |R |Provide any further         |
|RO/PP |13Feb |     |                      | |  |  |information
available (e.g.,|                                |      |      |
|                        | |  |  |single crystal x-ray        |
|     |     |     |                      | |  |  |
crystallographic studies,   |                                |      |
|     |                        | |  |  |moisture sorption isotherm  |
|     |     |     |                      | |  |  |studies, etc.)
from within  |                                |      |      |     |
| |  |  |your corporation or in the  |
|     |     |     |                      | |  |  |literature that
|                                |      |      |     |
| |  |  |characterizes the morphic   |
|     |     |     |                      | |  |  |forms or
hydrates of        |                                |      |      |
|                        | |  |  |oxycodone hydrochloride.    |
|     |     |     |                      | |  |  |
|Assemble technical team and set  |PP,   |21Jan |(On-g|Initial Mtg
held 15Jan   | |  |  |                          |up meeting to share
view with S  |SS, RO|      |oing)|                          | |  |  |
|Stoopak. Revisit Pharma vs.      |      |      |     |
| |  |  |                          |analytical approach.
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|      |      |     |                       | |3 |R |The solubility
data provided|                               |RO/PP |13Feb |     |
| |  |  |on the drug substance do not|
|      |      |     |                       | |  |  |demonstrate the
equivalence |                               |      |      |     |
| |  |  |of material from the three  |
|      |      |     |                       | |  |  |suppliers. The
data indicate|                               |      |      |     |
| |  |  |a lack of equivalence (e.g. |
|      |      |     |                       | |  |  |10.6 mg/ml at
pH 7.20 for   |                               |      |      |     |
| |  |  |Rhodes vs. 16.8 mg/ml at pH |
|      |      |     |                       | |  |  |7.24 for
Mallinckrodt).     |                               |      |     |
|                         | |  |  |                          |
|      |      |     |                       | |  |  |
|                             |      |      |     |
| |5 |R |Provide a satisfactory      |
|RO/PP |13Feb |     |                       | |  |  |explanation for
the multiple|                               |      |      |     |
| |  |  |exotherms or endotherms     |
|      |      |     |                       | |  |  |observed in the
differential|                               |      |      |     |
| |  |  |scanning calorimetry        |
|      |      |     |                       | |  |  |analysis of the
drug        |                               |      |      |     |
| |  |  |substance.                  |
|      |      |     |                       | |7 |R |Provide further
|                             |RO/PP/|13Feb |     |
| |  |  |characterization,           |
|SS    |      |     |                       | |  |  |clarification,
and as       |                               |      |      |     |
| |  |  |appropriate, specification  |
|      |      |     |                       | |  |  |to ensure a
consistent      |                               |      |      |
|                         | |  |  |morphic form of the drug    |
|      |      |     |                       | |  |  |substance (from
all         |                               |      |      |     |
| |  |  |suppliers) used in          |
|      |      |     |                       | |  |  |manufacture of
the drug     |                               |      |      |     |
| |  |  |product or provide a        |
|      |      |     |                       | |  |  |detailed
determination of   |                               |      |     |
|                         | |  |  |the effect of the           |
|      |      |     |                       | |  |  |variability of
the morphic  |                               |      |      |     |
| |  |  |form of the drug substance  |
|      |      |     |                       | |  |  |on drug product
performance,|                               |      |      |     |
```

			e.g., drug substance						aggregation, blend			
			uniformity,						dissolution/ bioavailability			
								|data (in addition to the			
								|dissolution study provided			
								|in the supplement), drug			
								|product stability, etc.			
									|T2 DP process validation report |SS/		
Fanast													
					i								
							Team to send comments to SS						
Team													
Final aggregate report due (#7, |SS |13Feb											
						|8d)							
Write separate paragraph to	PG												
						|discuss Light Microscopy based on|						
PP suggestion-crystal condition													
						|is a moot point-pre mill vs. post|						
milling.													
	DS Specifications												
	8a	R	The following comments refer										
FS/CL/	13Feb												
to the drug substance													
specification (release and													
stability):													
Provide revised acceptance													
criteria for impurities													
consistent with ICH Q3AR.													
							Provide description for DS Spec						
PG	30Jan												
(PP)													
							Alert CC Committee of priority						
of	AF	30Jan		Contacted LB on 1/27- on									
next CCC agenda													
DS Spec													
							Meet with P Cunningham to ensure						
JZ/CL	23Jan												

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|that existing DMF meets          |      |      |     |
| |  |  |                           |requirements—outcome will be
|      |      |     |                             | |  |  |
|relayed to team                  |      |      |     |
| |  |  |                           |Meet with Noramco to obtain
|CL    |Week  |     |                             | |  |  |
|agreement on proposed DS Spec    |      |of Feb|     |
| |  |  |                           |
|      |9     |     |                             | |  |  |
|Revised DS Spec to JK            |JL/KS |TBD   |     |
| |8e|R |The following comments refer|Need to discuss with all
|JK/RO/|13Feb |     |(FDA approved supplement | |  |  |to the drug
substance       |manufacturers                     |CL    |      |
|25Nov02 for bulk and     | |  |  |specification (release and  |
|      |      |     |tapped density)          | |  |  |stability):
|                                 |      |      |     |Issues
lingering with    | |  |  |                                 |
|      |      |     |Noramco. A response can  | |  |  |Provide
specifications for  |                                 |      |      |
|be drafted and reviewed. | |  |  |bulk density and tap density|
|      |      |     |Noramco was not aware    | |  |  |and provide
data and data   |                                 |      |      |
|they needed to provide   | |  |  |analysis, including test    |
|      |      |     |this. Noramco having     | |  |  |results for
batches use in  |                                 |      |      |
|issue with bulk density. | |  |  |appropriately characterized |
|      |      |     |Current Spec does not    | |  |  |drug product
batches (e.g., |                                 |      |      |     |
include Malvern.         | |  |  |validation batches), to     |
|      |      |     |                         | |  |  |support the
proposed        |                                 |      |      |
|                         | |  |  |specifications.             |
|      |      |     |                         | |1a|N |Provide a
revised drug      |Need agreement from Manufacturers|RO    |13Feb |
|                         | |1 |  |substance specification     |
|      |      |     |                         | |  |  |sheet
containing the        |                                 |      |
|     |                         | |  |  |following specifics:        |
|      |      |     |                         | |  |  |
|                                 |      |      |     |
| |  |  |Individual unspecified and  |
|      |      |     |                         | |  |  |unidentified
drug-related   |                                 |      |      |     |
| |  |  |impurity or degradation     |
|      |      |     |                         | |  |  |product: NMT
0.1%.          |                                 |      |      |     |
| |1a|N |Provide a revised drug      |Need agreement from
Manufacturers|RO    |13Feb |     |                         | |2 |  |
substance specification     |                                 |      |
|     |                         | |  |  |sheet containing the        |
```

								following specifics:			
								Total (Sum of all reportable			
			impurities and degradation								
								products >0.05%: NMT 2.0%.			
				1c	N	Provide a specification for	Need agreement from Noramco	JK/RO	13Feb		(FDA approved supplement		
			14Jan04 for particle				distribution (D10, D50, and			
size)				D90) using laser light							
								scattering technique that is			
				consistent with the							
								recommendations from the			
			pending supplement # 030.								
					8c	R	The following comments refer		RO/PP	13Feb	
			to the drug substance								
								specification (release and			
			stability):								
								Provide tightened acceptance			
								criteria for appearance (a			
			more detailed description,								
								e.g., crystal shape), assay			
			(98.0–102.0%), water content								
								(e.g. to be consistent with			
				oxycodone hydrochloride							
								monohydrate if appropriate),			
			residual solvents, and								
								particle size (e.g., two			
			sided limits for D90).								
								Provide justification for			
				the proposed specifications							
								(e.g., relationship to the			
				drug substance used in							

								critical drug product				
			biopharmaceutic, validation,									
								and stability batches).				
					Send out draft report to Jim							
SS	6Feb											
Kelly												
					Send out report to Team							
JK	6Feb							1d	N	Provide a specification or		
Team decided to have a				manufacturing controls to								
	(For		separate spec for Rhodes.									
effects of any										SS		
			potential agglomerates in									
	report									the drug substance on the		
										s		
					drug product (e.g. blend							
	refer									uniformity and in-process		
			content uniformity).							to		
	#1e)											
Check Storage sample data				JZ/PP	23Jan							
					(current inventory) for							
Mallinckrodt and Noramco												
	8d	R	The following comments refer									
SS/ PP	13Feb									to the drug substance		
										(For		
			specification (release and									
	SS									stability):		
					report							
			Provide a specification or									
	s									manufacturing process		
										refer		
			improvement to minimize the									
	to #7)									effect of any potential		
			agglomerates in the drug									
										substance on the drug		
			product (e.g., blend									
										uniformity and content		
			uniformity).									
Will we revise the USP monograph?	GVB	TBD								Process takes 1 year.		
			Future project-not an							And when?		
										immediate need.		

```
| |  |  |                           |File revised analytical method,
|RO/JK |13Feb |      |                           | |  |  |
|validation report in submission  |      |      |     |
| |DS Safety
| |8b|R |Provide safety qualification|Proceed with process related
|JP    |13Feb |      |[Mallinckrodt stated that| |  |  |of the
potentially genotoxic|approach                         |(RO)  |      |
|FDA based the 10ppm      | |  |  |drug substance impurities   |
|      |      |      |limits for ABUKs on the  | |  |  |with alpha-beta
unsaturated |                                 |      |      |     |
EPA's drinking water     | |  |  |ketone structures; e.g.,    |
|      |      |      |limits (Benzene etc).]   | |  |  |14-
hydroxycodeinone. Provide|                              |      |
|     |                         | |  |  |safety qualification either |
|      |      |      |                           | |  |  |via
demonstration that the  |                              |      |
|     |                         | |  |  |impurities are human        |
|      |      |      |                           | |  |  |metabolites or
via two in   |                                 |      |      |     |
| |  |  |vitro genotoxicity tests    |
|      |      |      |                           | |  |  |(one point
mutation assay   |                              |      |      |
|                         | |  |  |and one cytogenetic assay   |
|      |      |      |                           | |  |  |with the
isolated impurity  |                              |      |      |
|                         | |  |  |tested up to the limit doses|
|      |      |      |                           | |  |  |for each
assay). If no      |                              |      |      |
|                         | |  |  |safety qualification is     |
|      |      |      |                           | |  |  |submitted for
these        |                                 |      |      |     |
| |  |  |impurities, or if they are  |
|      |      |      |                           | |  |  |determined to
be genotoxic, |                                 |      |      |     |
| |  |  |limit each impurity to      |
|      |      |      |                           | |  |  |<0.001%.
|                                 |      |      |     |
| |  |  |                           |New 14-OH method has not  yet
|RO/   |6Feb  |      |[ Using the new 14-OH    | |  |  |
|been applied to previous Rhodes  |Bob   |      |     |method since
current     | |  |  |                           |batches- method can
reach 10ppm  |Chapma|      |     |codinone method would    | |  |  |
|and 500ppm.  Need to analyze 5   |n     |      |     |take up to 2
months to   | |  |  |                           |(T2 validation)
batches with new |      |      |     |validate for 14-OH.]     | |  |
|                         |method.  Ardsley can start work  |
|      |     |                         | |  |  |
|on 3 currently in house.         |      |      |     |
| |  |  |                           |Send prelim data from 3 batches
|JK    |6Feb  |      |                           | |  |  |
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|to Team                        |       |       |      |
| |  |  |                          |Provide comments/ resolve issues
|CL/JK |       |      |                          | |  |  |
|w/ Mallinckrodt                |       |       |      |
| |DS Documentation
| |6 |R |Provide more legible copies |Need to supply T2 data
|RO    |13Feb |      |                          | |  |  |of photographs,
certificates|                                   |       |       |      |
| |  |  |of analysis, and analytical |
|       |       |      |                          | |  |  |test results.
As                |                                 |       |       |      |
| |  |  |appropriate, standardize the|
|       |       |      |                          | |  |  |scales to
facilitate        |                                   |       |       |
|                          | |  |  |comparisons.                |
|       |       |      |                          | |  |  |
|Regenerate documents (PGoliber)  |RO/PG |13Feb |      |
| |  |  |                          |Provide API COAs
|KS    |10Feb |      |                          | |9 |R |DMF 16,399 has
been reviewed|                                  |CL/JK |       |      |
| |  |  |and has been found          |
|       |       |      |                          | |  |  |inadequate. A
deficiency    |                                 |       |       |      |
| |  |  |letter has been sent to the |
|       |       |      |                          | |  |  |holder of DMF
16,399 for    |                                 |       |       |      |
| |  |  |Oxycodone hydrochloride.    |
|       |       |      |                          | |  |  |
|Rhodes to submit Annual Report   |BL    |9Feb  |6Feb |
| |  |  |                          |for DMF
|       |       |      |                          | |1f|N |A deficiency
letter has been|                                  |CL/JK |       |      |
| |  |  |sent to the holder of DMF   |
|       |       |      |                          | |  |  |6318 for
oxycodone         |                                   |       |       |
|                          | |  |  |hydrochloride.              |
|       |       |      |                          | |  |  |
|Send DMF letter to JK            |CL    |23Jan |      |
| |  |  |                          |Redact letters from FDA for
|JK/CL |(26Jan|     |Upon signed CDA and      | |  |  |
|Noramco reference              |       |)      |      |receipt of
deficiency    | |  |  |                            |
|       |       |      |letter from Noramco      | |  |  |
|Noramco to submit DMF response to|(CL/JK|27Feb |      |
| |  |  |                          |FDA
|)     |       |      |                          | |  |  |
|Obtain a commitment and          |FS/CL |13Feb |6Feb |They will not
be signing.| |  |  |                           |non-disclosure
agreement from    |       |       |      |                          | |  |
|                            |Mallinckrodt and Noramco re:     |
```

ABUKS method					
			Noramco to provide flow chart and	CL	13Feb
mfg summary					
	DRUG PRODUCT				
	DP Specifications (Dissolution)				
	2b	N	Two past letters from the		
JK	28Feb				
			Agency (dated December 12,		
			2002, for the SN029 and June		
			20, 2003, for the SN031)		
			reminded you of providing		
			revised acceptance criteria		
			for dissolution. To date, no		
			response has been received		
			to this effect. Provide		
			tighter acceptance criteria		
			for dissolution consistent		
			with the Agency		
			recommendations.		
			DP Dissolution (Comparisons)		
	2a	N	Given the apparent		
LG	23Feb		(QA data audit issues to		
			(RO)	(Draft	
drug			substance morphic form, the		
managed by RO)			single medium dissolution f2		
	)		comparison provided in the		
			supplement is insufficient		
			supporting evidence for the		
			bio-equivalence of the drug		
			product manufactured with		
			Noramco drug substance from		
			the two sites and to the		
			drug product manufactured		
			from drug substance from		
			other vendors. Therefore,		
			provide f2 comparisons for		

							|the dissolution data from
							|multiple media covering all
							|pH ranges.
				Draft report to Team			
LG/RO	23Feb						
							|(Draft|
								)	
Team will review/comment				Team	EOB		
	24Feb						
LG will submit final signed /QA'd				LG	27Feb		
					report to team (JK)		
(RO)								4	R	Given the apparent								LG	23Feb
See previous question			|differences in drug			|substance			|action items			|single medium dissolution f2|		|comparison			|provided in the			|supplement (source and | | | |quality of drug substance | | | |batch used in manufacture of| | | |the reference drug product | | | |batch is not specified) is			|insufficient supporting			|evidence for the equivalence|		|of drug product manufactured|		|with Rhodes drug substance			|to drug product manufactured|		|with Mallinckrodt and			|Noramco drug substance.							|Finish f2 Report on T1:			
KS	10Feb						
T1 = 9 mos				T2 = 6 mos from Wilson			
Dissolution results to be				provided –report in progress			